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Combination of Echocardiographic and Pulmonary Function Test Parameters Improves Sensitivity for the Diagnosis of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension- Analysis of Two Cohorts

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Abstract

Objective—To evaluate routinely collected non-invasive tests from two systemic sclerosis (SSc) cohorts to determine their predictive value alone and in combination vs. right heart catheterization (RHC)- confirmed pulmonary arterial hypertension (PAH).

Methods—We evaluated two cohorts of patients who were at risk or with incident PAH: (1) The Pulmonary Hypertension Assessment and Recognition Outcomes in Scleroderma (PHAROS) cohort and (2) an inception SSc cohort at Cochin Hospital. Estimated right ventricular systolic pressure (eRVSP) on echocardiogram (TTE) and and pulmonary function tests (PFT) parameters were evaluated and their predictive values determined. We then evaluated patients with PAH missed on TTE cutoffs that were subsequently identified by a PFT parameter.

Results—In the PHAROS cohort (N=206), 59 (29%) had RHC-defined PAH. An eRVSP threshold of 35–50mmHg failed to diagnose PAH in 7–31% of patients, 50–70% of which (N=2–13) were captured by PFT parameters. In the Cochin cohort (N=141), 10 (7%) patients had RHC confirmed PAH. An eRVSP threshold of 35–50mmHg missed 0–70% (N = 0–7) patients, of which

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0–68% (N = 0–6) were captured by PFT parameters. The combination of TTE and PFT improved the negative predictive value for diagnosing PAH.

Conclusion—In 2 large SSc cohorts, screening with TTE and PFT captured majority of patients with PAH. TTE and PFT complement each other for the diagnosis of PAH.

Keywords

Echocardiogram; Pulmonary Function Tests; Screening; Diagnosis; Systemic Sclerosis; Pulmonary Hypertension; Pulmonary Arterial Hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) affects 5–15% of patients with systemic sclerosis (SSc) and is a leading cause of mortality (1–3). A meta-analysis of 3,818 patients showed a prevalence of PAH of 9% (95% CI 6%–12%) and identified advanced age, longer disease duration, and limited cutaneous disease subset as risk factors for this condition (4). Humbert *et al* recently showed improved survival in patients with PAH who were proactively screened and treated early during the course of their disease (2). However, the diagnosis of PAH is challenging as the symptoms (dyspnea at rest or with exertion, lower extremity edema, fatigue, dizziness and palpitations) usually overlap with other SSc-related manifestations (musculoskeletal involvement, de-conditioning, lung fibrosis) often leading to a delayed or missed diagnosis (5). Current guidelines for PAH screening recommend transthoracic echocardiogram (TTE) in SSc patients once yearly or when symptoms first occur (6–8), but do not refer to other screening modalities. Right heart catheterization (RHC) remains the gold standard for diagnosis of PAH with demonstration of a mean pulmonary artery pressure (mPAP) greater or equal to 25mmHg and a pulmonary capillary wedge pressure (PCWP) less than 15mmHg (9).

At present, only consensus-based guidelines exist for the screening and diagnosis of SSc-PAH. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend once yearly screening with TTE (6). The American College of Cardiology Foundation/American Heart Association also recommend yearly screening of patients with connective tissue disease (CTD) for PAH with TTE, but this recommendation was not evaluated for different subgroups of CTD (10). The lack of CTD or SSc- specific evidence based guidelines and the frequency of PAH in patients with SSc supports the importance of defining better screening and diagnosis methods.

We used two large cohorts of patients with SSc that were initially recruited with the goal of detecting patients at high risk of SSc-PAH. Our analysis had three primary objectives: 1. To assess the predictive values of estimated right ventricular systolic pressure (eRVSP) on TTE and Pulmonary function tests (PFT) parameters (ratio of forced vital capacity percent predicted to diffusion capacity of the lung for carbon monoxide percent predicted (FVC%/DLCO%); DLCO% predicted cut offs); 2. To identify patients who are captured by PFT parameters but are missed by eRVSP cut-offs; and 3. To assess predictors of PAH in the two cohorts when accounting for patient demographics, serum autoantibodies, eRVSP, and pulmonary function tests (FVC%/DLCO% ratio, and DLCO % predicted).

PATIENTS AND METHODS

Study population

We analyzed data on patients enrolled in a prospective study- the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort as of May

2009 (11, 12). PHAROS is a collaborative, multi-center study based in North America. It was established to prospectively follow two groups of patients with SSc (n=206) (defined according to the American College of Rheumatology classification) (13); those with PAH confirmed by RHC and those considered at high-risk for developing PAH (11). The entry criteria for patients at high-risk for PAH was to satisfy one of the following: 1) DLCO <55% predicted without severe interstitial lung disease (ILD); 2) FVC% predicted / DLCO% predicted ratio greater than 1.6; 3) eRVSP>40mmHg on TTE. Patients with pulmonary hypertension (PH) were excluded if left ventricular ejection fraction (LVEF) was less than 50% to exclude left sided systolic heart failure, or the PH was caused by other cardiopulmonary disease, drugs or toxins. Patients with PH on right heart catheterization were divided into World Health Organization (WHO) groups 1, 2, and 3 (14). Group 1 PH (or PAH) was defined by RHC hemodynamics of mPAP≥ 25mmHg and PCWP ≤ 15mmHg with an FVC ≥ 70% predicted and noneto-mild interstitial lung disease (ILD) on high resolution CT. Patients in Group 2 and 3 were excluded from the analysis.

The second cohort of 141 SSc patients consists of a prospective cohort of consecutive patients enrolled in the Paris Cochin Rheumatology cohort (Cochin cohort) aimed at evaluating SSc patients for PAH. Patients that had an eRVSP > 40mmHg on TTE, or DLCO <50% predicted in the absence of pulmonary fibrosis, or unexplained dyspnea underwent RHC for diagnosis of PAH.

Baseline demographics from both cohorts included age, SSc subtype (limited cutaneous systemic sclerosis [lcSSc] or diffuse cutaneous SSc [dcSSc]), race (Caucasian vs. non-Caucasian), time since diagnosis (first non-Raynaud's sign or symptom), autoantibody profile (anti-centromere antibody [ACA] and anti-topoisomerase antibody [ATA]), FVC%/DLCO%, DLCO% predicted, and eRVSP parameters. ACA and ATA were performed in the commercial laboratories in the PHAROS cohort. ACA was performed by immunofluroescence on HEP2 Cells and ATA was performed by counter immune-electrophoresis in the Cochin cohort. Neither cohorts had exclusion criteria for SSc specific medications. TTE was performed as part of routine clinical care.

STATISTICAL ANALYSIS

The PHAROS and Cochin cohorts were each evaluated alone and in combination. Student t-tests were conducted to determine any statistical difference between the two cohorts. In order to compare patients with RHC-confirmed PAH to those without RHC-PH, we examined the sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV) of eRVSP, FVC%/DLCO% and DLCO% predicted using various thresholds. Since one of the goals of our study was to identify optimal screening tests, we also assessed the NPV's of TTE and PFT parameters combined. Patients with RHC-confirmed PAH were also evaluated based on eRVSP, and the number of patients that were not detected as having PAH was computed to determine how useful various PFT parameters are in detecting PAH.

Finally, to determine the baseline demographic factors, autoantibodies, TTE and PFT results that can be used to diagnose and predict PAH, we performed univariate and multivariate logistic regressions on the two cohorts combined (15). $P < 0.05$ was considered indicative of statistical significance.

RESULTS

The PHAROS cohort had 206 patients compared to 141 in the Cochin cohort. The mean age of patients was 57.2 (SD 11.6, $p<0.01$) years in the PHAROS cohort as compared to 53.7 (SD 11.8, $p<0.01$) years in the Cochin cohort (Table 1). In the PHAROS cohort, patients had

longer disease duration (7.1 years vs 4.7 years, p<0.01), and only 14% were ATA positive as compared to 32% in the Cochin cohort (p<0.01).

In the PHAROS cohort, 59 subjects had WHO Class I PAH, 34 had PH secondary to ILD, 37 had PH secondary to left heart disease, 55 had no PH, and 21 patients could not be classified due to either missing FVC% predicted or missing PCWP data. This left 114 patients for current analysis (PAH [N=59] and without PH [N=55]). We excluded patients with PH secondary to left heart disease or secondary to ILD from analysis. In the Cochin cohort (N=141), 10 subjects had WHO Class I PAH, 5 had ILD-PH and 2 had PH secondary to left heart disease and 124 were without PH. The current analysis include 134 patients [10 with PAH and 124 without PH]., In patients with PAH (Table 1), the average eRVSP was lower in the Cochin cohort than in the PHAROS cohort (49.5mmHg vs. 61.5mmHg p=<0.01) and more were ATA positive (50% vs 5%, p<0.01). This difference in eRVSP is likely due to the increased number of patients with PAH in PHAROS, with 28.6% of patients with PAH as opposed to only 7.1% in the Cochin cohort.

The eRVSP on TTE and PFT (FVC%/DLCO%, DLCO%) were analyzed to determine the ability of various cut-offs to accurately predict PAH (Table 2). When combining the two cohorts, an eRVSP of >35mmHg resulted in a 58% PPV and 97% NPV as compared to an eRVSP >50mmHg that resulted in a PPV of 85% and NPV of 87% (Table 2), as the eRVSP threshold increased, the NPV decreased resulting in more cases of PAH being missed by eRVSP screening alone.

We also evaluated 2 PFT parameters (DLCO% predicted and the FVC%/DLCO% ratio) because of their known associations with PAH (16–19) (Table 2). In the two cohorts, a ratio of FVC%/DLCO% ≥ 1.6 had a 47% PPV and a 90% NPV whereas a ratio of FVC%/DLCO % ≥ 2.0 had a 65% PPV and a NPV of 85%. For DLCO% predicted in the two cohorts, DLCO%< 60% resulted in a 47% PPV and a 92% NPV (Table 2).

Because eRVSP had the highest PPV (Table 2), we determined the proportion of patients with RHC-PAH who were missed when using eRVSP cut offs but were captured by the PFT parameters (Table 3). In the PHAROS cohort, 55 (93%) of the 59 patients with RHC-PAH had an eRVSP >35mmHg and 4 (7%) had eRVSP≤ 35 mmHg. Of the four patients missed, two (50%) were captured by DLCO predicted <60% or FVC%/DLCO% ratio ≥ 1.6. In the Cochin cohort however, there were only 10 patients with RHC-PAH of which 100% were captured by an eRVSP > 35mmHg. As the eRVSP threshold increased, the number of patients with RHC-PAH that were missed increased simultaneously. Using as criteria eRVSP > 50mmHg, 18 (31%) patients in the PHAROS cohort with RHC-PAH were missed, of which 12 (67%) were captured by DLCO predicted <60% and 13 (72%) were captured by FVC%/DLCO% ratio ≥1.6. In the Cochin cohort, 7 (70%) patients were missed using eRVSP >50mmHg, however they were all captured when DLCO predicted <60% was used.

We developed a matrix of TTE and PFT parameters to assess if combination will improve the NPV (Table 4). By combining both TTE and PFT parameters we were able to improve the NPV over eRVSP or PFT parameters alone. With an eRVSP >50 mmHg, 36% of patients with PAH were missed, however combination of eRVSP >50 mmHg with FVC%/ DLCO% ≥1.6 captured 91% of patients (Table 4).

We next evaluated baseline demographics, clinical laboratory results, eRVSP, ratio of FVC %/DLCO% or DLCO% predicted for their ability of predicting PAH. For this goal, we fit a univariate logistic regression model (outcome variable: PAH vs. no PH) on the combined database comprising the two cohorts (N=248). A positive ACA increased the odds of having PAH, as well as having a greater FVC%/DLCO% ratio and having eRVSP > 40mmHg (Table 5). In contrast, the presence of ATA decreases the likelihood of having PAH (Table

5). In the multivariate logistic regression model (PAH vs. No-PH), the significant predictors for PAH were eRVSP>40mmHg (OR 29.2 [95%CI 11.2,76.3] and the ratio of FVC%/DLCO% ≥ 1.6 (OR: 2.89; [95%CI for OR [1.12; 7.46]]) after adjusting for age, disease duration, ACA and ATA (Table 6).

DISCUSSION

Patients with SSc have a high risk for development of PAH, and current guidelines recommend a yearly TTE or TTE at the appearance of symptoms in SSc (6, 7). Several cohort studies have suggested an eRVSP cut-off of 40mmHg (with calculated tricuspid velocity of 2.73–3.0 m/s, assuming right atrial pressure of 10mmHg), should be referred for RHC (20–23). However, TTE can be non-specific and can over or under estimate the eRVSP on RHC (24, 25). As such, better, more predictive non-invasive tests or combination of tests are needed to screen patients.

Previous studies have looked at a combination of non-invasive parameters for the diagnosis of PAH. However, none have evaluated the combination of PFT and TTE or PPV and NPV's of PFT and TTE for PAH. In a prospective study Meune *et al* proposed a composite score using PFT along with the patient's age to estimate the risk of developing PAH in SSc patients in the next 3 years. The authors developed the Cochin "Risk prediction score (RPS)" and validated it in a separate prospective study of 443 patients. In this study, a Cochin RPS of 2.73 had an 90% sensitivity and 74% specificity in the detection of patients developing PAH during follow-up (26). In another prospective cohort study, Allanore, et al. combined the ratio of DLCO to alveolar volume <70% with N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) level >97th percentile for age and found the combination to be 75% sensitive and 97% specific for PAH (27). In a case-control study, the authors used DLCO predicted <70.3%, FVC%/DLCO% ≥1.82 and NT-ProBNP ≥ 209.8pg/ml and found them to be 100% sensitive and 100% specific for SSc-PAH (28). A recently published prospective study assessed PFT's in combination with laboratory values and clinical characteristics in a stepwise algorithm with a cut-off score prompting TTE (29), and subsequent TTE cut-offs prompting RHC for screening of RHC-PAH.

Our study looked at two cohorts, and found that the combination of eRVSP on TTE and PFT parameters resulted in the detection of up to 97–100% of patients with RHC confirmed PAH. This is a vast improvement over using TTE alone for screening and early detection of PAH. Additionally, these criteria allowed to detect 31–70% of patients who were missed with an eRVSP>50mmHg but were later confirmed with RHC. The selected PFT parameters were chosen based on published studies suggesting that FVC%/DLCO% ratio greater than 1.6 or DLCO predicted <60% are strongly associated with PAH (16, 18, 29). Our data also confirms that FVC%/DLCO% ratio >1.6 is a reasonable cut-off for screening for PAH as it has a higher NPV than higher cut-off values (18, 29).

Early diagnosis and treatment of PAH in SSc patients is essential for an improved prognosis. Our results suggest that by using both TTE and PFT's patients with PAH can be identified with simple and worldwide available tests. By using both modalities, patients at risk of PAH are more likely to be identified by one of the non-invasive tests thus providing better rationale for RHC to confirm PAH and initiate treatment.

Our study has many strengths. Our study calculated predictive values of TTE and PFT parameters in two large SSc cohorts, which to our knowledge, has not been previously done in pure PAH cohorts. Mukerjee et al (2004) evaluated both PFT and TTE for the diagnosis of PH, however, TTE results did not exclude patients with ILD (16). We have provided a

matrix of eRVSP and PFT parameters that show how the combination of these two parameters results in an increased NPV.

However, our study is not without limitations. The PHAROS database did not have routine collection of NT-ProBNP or brain natriuretic peptide (BNP), which have been shown to be predictive for PAH (30, 31) in SSc. In addition, we only focused on eRVSP on TTE, since we did not have additional TTE data, including tricuspid pulmonic gradient or tricuspid annular plane systolic excursion (TAPSE) or right chamber enlargement, both shown to be associated with PAH. Mathai et al. evaluate TAPSE in SSc-PAH and found that TAPSE is a sensitive and reproducible measure of RV function and was associated with other measure of RV function in a large cohort (32).

In conclusion, we show that screening with TTE and PFT captured majority of patients with SSc-PAH. TTE and PFT complement each other for the diagnosis of SSc-PAH. We recommend the use of both TTE and PFT for screening of SSc-PAH.

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TABLE 1

Baseline data for the PHAROS and Cochin databases.

	PHAROS (N=206)	COCHIN (N=141)	p-value	PHAROS PAH (N=59)	COCHIN PAH (N=10)	p-value
Age yrs, mean (SD)	57.2 (11.6)	53.7 (11.8)	<0.01	62.4 (10.3)	63.1 (12.9)	0.87
% female	85.1	84.0	0.78	88.0	60.0	0.08
% lcSSc	62.6	56.0	0.22	78.0	60.0	0.27
% Caucasian	69.6	93.0	<0.01	83.0	100.0	<0.01
ACA+ (%)	21.0	22.0	0.82	41.0	20.0	0.14
ATA+ (%)	14.0	32.0	<0.01	5.0	50.0	<0.01
Time since diagnosis (yrs), mean (SD)	7.1 (8.1)	4.7 (6.7)	<0.01	8.0 (10.1)	9.9 (8.6)	0.53
Non-RP symptom (yrs), mean (SD)	8.7 (7.3)	NA	NA	9.4 (8.9)	NA	NA
% DLCO, mean (SD)	40.6 (16.1)	71.3 (20.6)	<0.01	43.1 (17.8)	38.6 (7.8)	0.19
FVC % predicted, mean (SD)	74.7 (20.1)	94.0 (20)	<0.01	87.9 (12.95)	82.6 (10.4)	0.16
eRVSP (mmHg), mean (SD)	53.0 (21)	31.6 (9.9)	<0.01	61.5 (20.2)	49.5 (6.8)	<0.01

lcSSc (limited cutaneous systemic sclerosis), ATA (Anti-topoisomerase Antibody), ACA (Anti-centromere antibody)

TABLE 2

Positive and negative predictive values of TTE and PFTs at detecting PAH

	PHAROS N=114				Cochin N=134				ALL N=248			
	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec
eRVSP>35mmHg	0.63	0.85	0.93	0.42	0.38	1.0	1.0	0.87	0.58	0.97	0.94	0.73
eRVSP>40mmHg	0.69	0.79	0.85	0.60	0.71	1.0	1.0	0.97	0.70	0.94	0.87	0.85
eRVSP>45mmHg	0.74	0.75	0.78	0.71	0.83	0.96	0.50	0.99	0.75	0.90	0.74	0.91
eRVSP>50mmHg	0.84	0.72	0.69	0.85	1.0	0.95	0.30	1.0	0.85	0.87	0.64	0.96
FVC%/DLCO%≥1.6	0.53	0.52	0.80	0.24	0.30	0.99	0.90	0.83	0.47	0.90	0.81	0.65
FVC%/DLCO%≥1.8	0.56	0.56	0.71	0.40	0.38	0.98	0.80	0.90	0.52	0.88	0.72	0.74
FVC%/DLCO%≥2.0	0.68	0.62	0.61	0.69	0.50	0.97	0.60	0.95	0.65	0.85	0.61	0.87
DLCO% < 70	0.50	0.25	0.90	0.04	0.18	1.0	1.0	0.63	0.39	0.93	0.91	0.45
DLCO% < 60	0.50	0.38	0.83	0.11	0.36	1.0	1.0	0.85	0.47	0.92	0.86	0.63
DLCO% < 50	0.55	0.56	0.75	0.35	0.50	0.99	0.90	0.93	0.54	0.89	0.77	0.75

PPV= positive predictive value, NPV= negative predictive value, Sens= sensitivity, Spec= specificity, eRSVP= estimated right ventricular systolicpressure in mmHg, FVC/DLCO= Forced vital capacity/ diffuse of the lung for carbon monoxide percent predicted ratio, DLCO= diffusion capacity for the lung percent predicted

Table 3

Patients captured by TTE and PFT parameters in the two cohorts.

eRVSP on TTE (mmHg)	Total (N) meeting TTE criteria	Missed by TTE threshold N (%)	N(%) missed by TTE and captured by DLCO < 60	N (%) missed by TTE and captured by ratio ≥ 1.6
PHAROS	N=59			
> 35	55	4 (7)	2 (50)	2 (50)
> 40	50	9 (15)	7 (78)	7 (78)
> 45	46	13 (22)	9 (69)	9 (69)
> 50	41	18 (31)	12 (67)	13 (72)
Cochin	N=10			
> 35	10	0 (0)	0(0)	0(0)
> 40	10	0 (0)	0(0)	0(0)
> 45	5	5 (50)	5 (100)	4 (80)
> 50	3	7 (70)	7 (100)	6 (86)

eRVSP= estimated right ventricular systolic pressure in mmHg

FVC/DLCO= Forced vital capacity/diffuse of the lung for carbon monoxide percent predicted ratio, DLCO= diffusion capacity for the lung percent predicted

Table 4

Positive and Negative predictive values of combination of TTE and PFT parameters

	eRVSP>35mmHg				eRVSP >40mmHg				eRVSP > 45mmHg				eRVSP > 50mmHg			
PFT parameters	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec
FVC%/DLCO%≥1.6	0.433	0.978	0.970	0.512	0.508	0.982	0.970	0.638	0.508	0.966	0.940	0.649	0.513	0.951	0.910	0.669
FVC%/DLCO%≥1.8	0.455	0.980	0.970	0.551	0.546	0.984	0.970	0.689	0.553	0.969	0.940	0.707	0.560	0.948	0.896	0.730
FVC%/DLCO%≥2.0	0.492	0.982	0.970	0.615	0.643	0.986	0.970	0.793	0.655	0.947	0.882	0.822	0.687	0.937	0.851	0.851
DLCO < 60%	0.436	0.978	0.970	0.517	0.500	0.982	0.970	0.626	0.500	0.965	0.940	0.649	0.508	0.966	0.940	0.649
DLCO < 70%	0.369	0.969	0.970	0.362	0.406	0.975	0.970	0.454	0.403	0.963	0.955	0.454	0.408	0.964	0.955	0.465

eRVSP= estimated right ventricular systolic pressure in mmHg FVC/DLCO= Forced vital capacity/diffusion of the lung for carbon monoxide percent predicted ratio, DLCO= diffusion capacity for the lung percent predicted. PPV= positive predictive value, NPV= negative predictive value, Sens= sensitivity, Spec= specificity.

Table 5

Univariate logistic regression for association with PAH

	N	OR	95% CI	p-value
Age	247	1.08	[1.05; 1.1]	< 0.001
Female	247	0.8	[0.4; 1.7]	0.58
SSc disease duration	244	1.06	[1.0; 1.1]	0.001
ACA	236	2.78	[1.5; 5.2]	0.001
ATA	235	0.41	[0.2; 0.9]	0.03
TTE (continuous)	241	1.17	[1.1; 1.2]	< 0.001
FVC%/DLCO% (continuous)	246	4.93	[2.8; 8.6]	< 0.001
eRVSP>40mmHg	241	40.28	[17.7; 91.8]	< 0.001
FVC/DLCO ≥ 1.6	246	8.19	[4.2; 16.1]	< 0.001

ACA= Anticentromere antibody, ATA= Anti-topoisomerase antibody, TTE= transthoracic echocardiogram in mmHg, eRVSP= estimated right ventricular systolic pressure, FVC%/DLCO%= Forced vital capacity/diffuse of the lung for carbon monoxide percent predicted ratio

Table 6

Multivariate logistic regression for association with PAH

	OR	95% CI	p-value
Age	1.04	[0.996; 1.09]	0.07
SSc disease duration	0.99	[0.93; 1.05]	0.78
ACA	1.54	[0.53; 4.42]	0.43
ATA	0.53	[0.16; 1.79]	0.31
eRVSP>40mmHg	29.34	[11.26; 76.41]	< 0.001
FVC/DLCO ≥ 1.6	2.98	[1.16; 7.66]	0.02

ACA= Anticentromere antibody, ATA= Anti-topoisomerase antibody, eRVSP= estimated right ventricular systolic pressure, FVC%/DLCO%= Forced vital capacity/diffuse of the lung for carbon monoxide percent predicted ratio